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Abstract

Inter-individual differences in drug response are an important cause of failure in anticancer treatment and adverse drug events in cancer patients. Gene polymorphisms related to these outcomes have been investigated in an effort to find new genetic biomarkers to predict toxicity and response to anticancer drugs. Evaluating the value single nucleotide polymorphisms (SNPs) in the genes involved in transportation, activation and metabolism of anticancer drugs provides a promising approach to select the appropriate therapeutic regimes with at least adverse reactions. This review summarizes the current knowledge about the relationship between of SNPs involved in the transportation, activation and metabolism of anticancer drugs and treatment outcomes in colorectal cancer (CRC) patients.

Key words: colorectal cancer, polymorphisms, anticancer drugs, Pharmacogenetics

Introduction

Colorectal cancer (CRC) is one of the most common causes of cancer related death globally (Moradi-Marjaneh, Hassanian et al. 2017). Chemotherapeutic drugs, radiation therapy and surgical resection are approaches to improve the patient's survival rate(Bahrami, Hassanian et al. 2017). Despite advances in the treatment of CRC, a large percentage of patients still die of the disease(Rahmani, Avan et al. 2017). The treatment outcomes vary. Additionally, adverse drug reactions are very variable, so that some patients successfully complete treatment cycles, whilst in others treatment must be discontinued due to life threatening complications(Plumpton, Roberts et al. 2016). Therefore, there is an urgent need to identify biomarkers that are able to tailor an appropriate drug for the CRC patient.

The importance of pharmacogenetics in the drug management of CRC patient was not recognised for a long time, but there has been a recent interest in personalized medicine. Pharmacogenetics is promising for the identification of patients with a high risk of side effects, and to design an effective treatment regime based on individual's characteristics(Bruun, Eide et al. 2017). Single Nucleotide Polymorphisms (SNPs) may play an important role in the identification of susceptibility to various diseases and responses to treatment(Wheeler, Maitland et al. 2013). The identification of specific SNPs from the large number that has the potential for predicting treatment outcomes and possible toxicity is manifestly essential before using them in clinic. For this purpose, candidate-gene association studies have been a useful approach to identify some of these variants. Genome-wide association studies (GWAS) also have a value in identifying the variants and their association with treatment outcomes(Fernandez-Rozadilla, Cazier et al. 2013).

The efficacy and toxicity of anticancer drugs in cancer cells depend on various factors, including the effective concentration of drug in the cell and the efficiency of enzymes activating/metabolizing anticancer drug. The effective concentration of anticancer drug in cancer cells is dependant on the cell membrane transporters(J Liu, Lu et al. 2012). In addition, many anticancer drugs are not potentially

active and enzymes responsible for drug activating are needed. Also, the toxicity of the systemic administration of therapy is influenced by the processes involved in the metabolism of the drug(Mitselou, Ioachim et al. 2012, Dean 2016).

The aim of this study was to summarize the genetic variation in genes which their products regulate the activation, metabolism and concentration of CRC anticancer drugs in cancer cells, in order to introduce informative polymorphism markers such as SNPs for implementation into clinical use as a assisting to select the best chemotherapeutic strategy for CRC patients with the most sensitivity and the least toxicity.

SNPs of genes involved in Anticancer Drug Transporter

Membrane transporters proteins including ATP-binding cassette (ABC) and the solute carrier (SLC), play an important role in processes involved in anti-cancer drug pharmacokinetic; absorption, distribution, metabolism and elimination or excretion (ADME). In addition there has been increasing evidence that ABCs and SLCs play an important role in the biology of various cancers including CRC. ABCs and SLCs are also strongly involved in multi-drug resistance (MDR)(Januchowski, Zawierucha et al. 2013). Low accumulation of anti-cancer drugs in cancer cells may be as a result of drug efflux, mediated by ABC transporters, or decreased drug uptake into the cancer cells, mediated by SLC transporters(De Mattia, Toffoli et al. 2013).

There is growing evidence showing the importance of single nucleotide polymorphisms (SNPs) of ABCs and SLCs in determining inter-interindividual differences of pharmacokinetics of a variety of anti-cancer drugs(Ab Mutalib, Yusof et al. 2017). This variability is also related to significant differences in treatment outcome and severe unpredictable toxicity in some patients(Di Martino, Arbitrio et al. 2011).

ATP-binding cassette (ABC) transporters

ATP-binding cassette (ABC) transporters mediate multidrug resistance (MDR) through chemotherapeutic drugs efflux(Wu, Kang et al. 2013). There is growing evidence indicates that the analysis of polymorphism in ABC genes could be employed as a potential approach to predict

chemotherapy outcomes and possible toxicity in CRC patients. A case–control study has evaluated the relationship between ABCB1 polymorphisms and risk of CRC and clinical outcomes following chemotherapeutic regimes in 1028 CRC patients and 1230 controls. The CT rs1045642 and GT/A rs2032582 SNPs were associated with an increased risk of CRC. In addition the TT rs1128503-TT rs2032582-TT rs1045642 haplotypes were associated with worse PFS. But the presence of the CT rs1128503 SNP was related to a longer OS after oxaliplatin-based chemotherapy(Wu, Kang et al. 2013)

A further study confirmed that genetic variations in ABCB1 are related to early toxicity and lower response to irinotecan and 5-FU treatment. So that TTrs1045642 was related to an increased risk of early toxicity in irinotecan and 5-FU-treated CRC patients. Also carriers of the T rs1128503-T rs2032582-T rs1045642 haplotype were less sensitive and had shorter OS(Glimelius, Garmo et al. 2011). Patients with the homozygous genotype of CC rs562 in ABCC5 gene and GG rs425215 in ABCG1 gene had an increased susceptibility to gastrointestinal toxicity following irinotecan therapy in metastatic CRC patients(Di Martino, Arbitrio et al. 2011). Mattiaa et al indicate that C>T rs7699188 polymorphism in ABCG2 gene and G>T/A rs2032582 polymorphism in ABCB1 gene are predictive of the response to treatment and patient OS respectively(De Mattia, Toffoli et al. 2013). Also the CC rs717620 in ABCC2 gene was found o be related to longer PFS and efficacy of first-line FOLFIRI in advanced CRC patients(Akiyama, Fujita et al. 2012). In addition carriers of GT rs2032582 ABCB1 gene who received irinotecan monotherapy or irinotecan–cisplatin-combination had higher SN-38 (active metabolic of irrinotecan) levels (Sai, Saito et al. 2010).

Contrary to the results of the above studies, Falkowski et al did not find any associations between CRC and SNPs in ABCB1 and ABCC2 genes in 300 CRC patients and 300 matched controls. but, they did report a relationship between environmental risk factors and CRC so that carriers of ABCB1 rs1045642-T (exon26) variant allele in the subgroup that had never consumed alcohol had an increased risk of CRC (Falkowski, Woillard et al. 2017). Custodio et al study also showed a significant association between polymorphisms of rs1045642 in ABCB1 gene and rs2231142, rs2728124 and rs3114018 in ABCG2 gene

and outcome of chemotherapy in patients with stage II and III colon cancer(Custodio, Moreno-Rubio et al. 2014). Another study evaluated the relationship between rs1045642 and risk of recurrence in CRC patients treated by 5FU and leucovorin and did not find any correlation(Huang, Fang et al. 2008).

Kap et al design a model of 1,444 SNPs to find a predictive markers for oxaliplatin treatment. Finally they chose 14 SNPs from eight genes (ABC transporters, ATPases and Metabolizers). Minor alleles of rs1642763 in ATP1B2 gene, rs8100856 in ATP8B3 gene and rs11807 in GSTM5 gene were associated with an increased risk of death in the patients who treated with oxaliplatin, while the contrary association was observed in patients who were not treated with oxaliplatin. Carriers of the minor allele of rs2125739 in ABCC10 gene and rs7249302 in ATP8B3 gene who received oxaliplatin had a small risks of mortality (Kap, Seibold et al. 2016).

Solute carrier (SLC) transporters

The organic-anion-transporting polypeptide (OATP/SLCO) gene belongs to the SLC transporter gene family. It has been proposed that the OATP/SLCO polymorphisms can be used to predict the treatment outcomes in CRC patients. The solute carrier organic anion transporter family member 1B1 (SLCO1B1) gene encodes for a protein called organic anion transporting polypeptide 1B1 (OATP1B1)(Romaine, Bailey et al. 2010). The heterozygous genotype of GA rs2306283 in OATP1B1/SLCO1B1 was related to increased gastrointestinal toxicity following irinotecan therapy in patients with metastatic CRC (Di Martino, Arbitrio et al. 2011). Furthermore Huang1 et al selected 3 SNPs in SLCO/ OATP gene and genotyped 137 metastatic CRC patients. They showed that GA/AA rs2306283 in SLCO1B1 gene and GG rs1051266 in SLC19A1 gene were associated with a higher rapid response rate. GA/AA rs2306283 in SLCO1B1 gene was also an independent prognostic factor for a longer PFS(Huang, Zhang et al. 2013). However Falkowski et al did not find any association between variant genotypes of SLCO1B1 and 2B1 and CRC(Falkowski, Woillard et al. 2017).

SNPs of genes involved in activation and metabolism of chemotherapeutic drugs.

Studies on the variants of genes involved in activation and metabolism of chemotherapeutic drugs have provided promising evidences to predict the outcome of treatment and drug response, as well as the potential for toxicity following chemotherapy.

DPYD

Dihydropyrimidine dehydrogenase (DPD) is a rate-limiting enzyme in the pathway of uracil and thymidine catabolism. DPD catabolizes approximately 85% of 5-FU in CRC patients receiving 5-FU and defects in its function increases the risk of 5-FU toxic accumulation. Molecular defects of DPYD gene lead to the deficiency of DPD activity(Dean 2016). Studies on DPYD gene polymorphisms provide promising evidences to predict toxicity following chemotherapeutic regimes in CRC patients. Graziano et al in the randomized phase III TOSCA trial analyzed 9 DPYD polymorphisms in 195 CRC patient who were treated with either FOLFOX-4 or XELOX for 3 or 6 months. The interval between the onset of treatment and the first severe toxicity was shorter with GA rs1801160 compared to GG genotype and GA rs3918290 compared to GG genotype for neutropenia. Also it was in a shorter timescale with CT rs1801265 genotype compared to TT genotype for diarrhea and was longer in presence of allele C (TC or CC) conferred for neurotoxicity(Graziano, Ruzzo et al. 2016). Also a novel mutation 464 T>A was identified in DPYD gene by Morel et al which was related to severe diarrhea, mucositis, leucopoenia, thrombocytopenia, and dehydration(Morel, Boisdron-Celle et al. 2007) .

Meulendijks et al undertook a meta-analysis of the results of 8 studies including 7365 patients from eight studies. They report that DPYD c.1679T>G (rs55886062) and c.1236G>A/HapB3 (rs56038477) was significantly related to fluoropyrimidine-associated gastrointestinal and hematological toxicity. They recommended screening of DPYD variants c.1679T>G and c.1236G>A/HapB3 to improve the safety of patients who treated with fluoropyrimidines(Meulendijks, Henricks et al. 2015). Lee et al genotyped 2886 patients with stage III colon cancer received FOLFOX or FOLFIRI regimes alone or combined with cetuximab. They showed an association between DPYD variants and adverse event (AE); the rs3918290

SNP was associated with specific AEs including nausea/vomiting and neutropenia whereas rs67376798 was associated with dehydration, diarrhea, leukopenia, neutropenia and thrombocytopenia(Lee, Shi et al. 2014).

TYMS & TYMP & TS

Thymidylate synthetase (TYMS) and thymidine phosphorylase (TYMP) are fluorouracil-associated enzymes. It has been shown that overexpression of TYMS is associated with resistance to 5-FU chemotherapy and may lead to poorer DFS and OS(Koumarianou, Tzeveleki et al. 2014). TYMP play a role in regulation of pyrimidine metabolism in the cell. Evidences show that TYMP plays an important role in angiogenesis and extracellular matrix remodeling(Mitselou, Ioachim et al. 2012).

There was no relationship between TYMS double or triple tandem repeats and early recurrence of CRC in patients treated by 5-FU and leucovorin (Huang, Fang et al. 2008). A meta-analysis study of 2402 CRC patients for the most commonly studied SNP of TYMS, rs45445694 and indicated that the rs45445694 SNP is associated with effects on protein expression, clinical benefit and adverse effects. However, the clinical utility limited because of the effect size was small(Jennings, Kwok et al. 2012).

Thymidylate synthase (TS) is an important target for 5-FU; it is inhibited by FdUMP. FdUMP forms a stable ternary complex with TS and methyl-tetra-hydrofolic acid (MTHF/CH2THF). TS down-regulation improve the efficacy of the 5-FU(Ijichi, Adachi et al. 2014). Sarasqueta et al genotyped variable number of SNPs of TS gene in 251 patients with stage III colon carcinoma, but they indicated that TS gene polymorphisms is not a good candidate to predict the outcome of 5-FU treatment(Farina-Sarasqueta, Gosens et al. 2010). But another study showed that TS-3'-UTR -6/-6 carriers had a significantly longer OS in comparison with other genotype following modified FOLFOX6 treatment(Kumamoto, Ishibashi et al. 2013).

UGT & Top1

Two important enzymes involved in metabolism and activation of irinotecan are UDP glucuronosyltransferase (UGT) and Topoisomerase 1 (Top1) respectively. UGT is a cytosolic glycosyltransferase enzyme that catalyzes glucuronidation reaction. Glucuronidation is the main metabolic pathway of irinotecan (CPT-11) and has been shown to protect against its toxicity. Responsible of irinotecan induced toxicity is SN-38 (7-Ethyl-10-hydroxycamptothecin) that is the pharmacologically active metabolite. UDP-glucuronosyltransferase1A (UGT1A) is the main enzyme involved in the glucuronidation of SN-38 to inactive metabolite, SN-38G. Evidences show that SNPs of UGT1A are important factors in irinotecan metabolism and are associated with higher rates of irinotecan related toxicity including neutropenia(Goetz, McKean et al. 2013). McLeod et al showed an association between the homozygous UGT1A1*28 allele and severe neutropenia in 520 advanced CRC patients who treated with irinotecan plus oxaliplatin (IROX)(McLeod, Sargent et al. 2010). Similarity Lévesque et al showed that three SNPs located in the central region of UGT1A are related to neutropenia after irinotecan therapy. They propose that these SNPs a are used for pharmacogenetic testing(Lévesque, Bélanger et al. 2013). Also another study showed an association between the homozygous UGT1A1*28 allele and severe neutropenia in patients who treated with irinotecan plus oxaliplatin (IROX)(McLeod, Sargent et al. 2010). However Falkowski et al did not find any associations between CRC SNPs in UGT1A6–9 and UGT2B7 genes (Falkowski, Woillard et al. 2017). But they found a relationship between UGT1A8 rs1042597-G, environmental risk factors and CRC so that carriers of the UGT1A8 rs1042597-G variant allele in the subgroup of meat-consumers had an increased CRC risk(Falkowski, Woillard et al. 2017).

Marcuello1 et al designed a trial with the aim of determining the maximum tolerated dose of irinotecan according to UGT1A1 genotype. The maximum dose tolerated by patients was 450 mg/m2 in patients with the UGT1A1*1/*1 genotype, 390 mg/m2 in patients with the UGT1A1*1/*28 genotype, but only to 150 mg/m2 in patients with the UGT1A1*28/*28 genotype. Significantly lower response rates (RR) was observed in patients with UGT1A1*28/*28 genotype (13%) in comparison with UGT1A1*1/*1

(60%) and UGT1A1*1/*28 (39%) (Marcuello, Paez et al. 2011). However Dias et al perform a systematic review and meta-analysis to analyze the association between different UGT1A1*28 genotypes and objective response rate (ORR) in irinotecan-administered cancer patients. They showed that UGT1A1*28 polymorphism is unlikely factor to effect on response to irinotecan(Dias, McKinnon et al. 2012).

Topoisomerase 1 (Top1) is an enzyme inhibits by irinotecan. It is an essential nuclear enzyme involved in DNA replication, transcription, translation, recombination and repair. Paolicchi analyzed two SNPs of Topoisomerase 1 (topo-1) gene including rs6072249 and rs34282819 to find the benefit from irinotecan in mCRC patients, but they find no correlation with clinical parameters (OS and PFS)(Paolicchi, Vivaldi et al. 2016)

GSTM1 & GSTP1

Glutathione S-transferase Mu 1 (GSTM1) and Glutathione S-transferase P (GSTP1) belong to the Glutathione S-transferase family that play an important role in detoxification compounds including carcinogens, therapeutic drugs and toxins. GSTM1 and GSTP1 genetic variations play a role in susceptibility to cancer, as well as effect on toxicity and efficacy of chemotherapeutic drugs(Sharma, Singh et al. 2015). Deletion in GSTM1 was related to severe neutropenia and GSTP1 homozygous variant genotype was related to neurotoxicity after FOLFOX therapy in CRC patients(McLeod, Sargent et al. 2010).

The copy number of GSTM1 DNA is associated with survival in CRC patients treated with chemotherapy; so that mortality was significantly decreased in patients with one GSTM1 copy and non-significantly decreased in those with the null genotype in comparison with carriers of two copies(Funke, Timofeeva et al. 2010).

Sarasqueta et al showed that the A>G rs1695 polymorphism in the GSTP1 gene is more frequent in men than in women. They indicated that AA rs1695 in GSTP1 gene may have a prognostic value in male CRC

patients treated with oxaliplatin. So that homozygous AA rs1695 in men had significantly worse cancer-specific survival and OS than women with the same genotype. However they suggested that SNPs in GSTP1 gene are not a reliable marker of the response to oxaliplatin therapy(Sarasqueta, van Lijnschoten et al. 2011). Similarity Le Morvan et al indicated that rs1695 in GSTP1 gene had no association with event-free and OS in patients treated by oxaliplatin or irrinotecan based chemotherapy(Le Morvan, Smith et al. 2007). Also Zaanan et al did not observed any association between GSTP1 polymorphisms rs1695 and DFS(Zaanan, Dalban et al. 2014). Another study confirmed that the rs1695 is not a reliable marker for predicting treatment outcomes in patients with CRC(Huang, Fang et al. 2008). In addition a meta-analysis in twelve prospective trials and two retrospective clinical trials (sample size: 2,191) showed no significant correlation between rs1695 and oxaliplatin-induced neuropathy(Peng, Wang et al. 2013).However McLeod et al indicated that AArs1695 carriers are more likely to discontinue FOLFOX because of neurotoxicity(McLeod, Sargent et al. 2010). Also another study showed that AArs1695 carriers had poor responses to mFOLFOX6 treatment in comparison with A/G & G/G genotypes(Kumamoto, Ishibashi et al. 2013).

SNPs of genes involved in DNA repair and synthesis

DNA excision repair protein (ERCC-1) and X-ray repair cross-complementing protein 1(XRCC1) are two proteins that are involved in DNA repair. ERCC1 is combined with ERCC4 to form a complex that participates in DNA repair and DNA recombination. Also XRCC1 is a scaffolding protein interacts with multiple repair enzymes(Carrera-Lasfuentes, Lanas et al. 2017).

The CC rs11615 polymorphism in the ERCC1 gene and GG rs25487 in XRCC1 gene are associated with a better PFS and OS respectively in CRC patients. In addition, the carriers of both of these genotypes have better PFS and OS than those with only one or any of them.(Huang, Huang et al. 2011). Conversely Zaanan et al showed that carriers of TC/T rs11615 in ERCC1 gene versus CC and AA rs25487 in XRCC1 gene versus GG/A had longer disease-free survival (DFS). Also carrier patients at least one variant allele

in rs1052559 in ERCC2 gene who treated with oxaliplatin based chemotherapy had shorter OS than those having no variant allele(Le Morvan, Smith et al. 2007). A combination of favorable genotypes showed better result in DFS(Zaanan, Dalban et al. 2014). Also Sarasqueta et al showed that A>C rs13181 in ERCC2 gene is more frequent in women than in men, but they indicated that none of the polymorphism in ERCC2 gene had effect on disease-free survival following oxaliplatin therapy(Sarasqueta, van Lijnschoten et al. 2011). But another study showed that the median PFS of AArs13181 carrier tended to be longer than ACrs13181 carrier in 63 CRC patients who received modified FOFOX(mFOLFOX)(Kumamoto, Ishibashi et al. 2013)

Methylene tetrahydrofolate reductase (MTHFR) is the rate-limiting enzyme in the methyl cycle, involved in DNA synthesis. It has been shown that TT rs1801133 carriers are at an increased risk for CRC (Bailey 2003). Custodio et al performed genotyping of 32 genes involved in chemotherapeutic drug response for 67 SNPs in tumor samples of CRC patients receiving oxaliplatin-based chemotherapy. They showed that the combination of TT rs1801133 and G>A G/G rs3917412 genotypes in MTHFR and selectin E (SELE) respectively is related to increased risk for recurrence(Custodio, Moreno-Rubio et al. 2014). However Huang et al did not show any relationship between C>T rs1801133 and risk of CRC recurrence in 201 CRC patients treated by 5-FU and leucovorin (Huang, Fang et al. 2008).

SNPs and their lack of association with clinical outcomes in CRC

In spite of the results of studies that indicate SNPs are related to clinical outcomes of CRC, there are other studies that indicate there is no relationship. This emphasizes the importance of further investigation in this issue. It seems that GWAS in different populations have a good response to drug selection and dose based on hereditary features(Fernandez-Rozadilla, Cazier et al. 2013).

Falkowski et al investigated associations between CRC and Fifteen SNPs in UGT1A6–9, UGT2B7, ABCB1, ABCC2, SLCO1B1 and SLCO2B1 genes and correlated them with environmental risk factors in 300 CRC patients and 300 matched controls. There was no significant evidence of an association between the

analyzed SNPs and risk of CRC. (Falkowski, Woillard et al. 2017). Gerber et al also performed quantitative genotyping of 16 SNPs including rs10411210, rs10936599, rs11169552, rs16892766, rs3802842, rs4444235, rs4779584, rs4939827, rs6687758, rs6691170, rs6983267, rs7014346, rs7136702, rs719725, rs961253, rs9929218 in 194 paired CRC and normal DNA samples for discovery set and 296 paired for validation set. These SNPs showed statistically significant association with CRC in published GWAS. But their results indicated that there was no statistically significant evidence for allele-specific somatic selection. However, the G allele of rs6983267 belong to cancer susceptibility 8 (CASC8) gene was related to significant evidence of relative retention(Gerber, Hampel et al. 2012). Furthermore Kanai et al investigate the association between severity of peripheral sensory neuropathyand (PSN) and 12 SNPs (rs3114018 (ABCG2), rs843748 (ACYP2), rs4936453 (BTG4), rs2230641 (CCNH), rs12023000 (CAMK2N1), rs797519 (DLEU7), rs17140129 (FARS2), rs2338 (FOXC1), rs1695 (GSTP1), rs830884 (ITGA1) and rs10486003 (TAC1), rs25487 (XRCC1)) in a prospective pharmacogenomics study in 84 Japanese patients who failed to complete FOLFOX therapy. Their result shows no clinical significant between PSN and any of the 12 SNPs(Kanai, Kawaguchi et al. 2016). McLeod et al extracted germline DNA from 520 advanced CRC patients and 34 variants in 15 genes were assessed for adverse events or treatment outcome. They did not confirm most previously published genotype toxicity or efficacy association(McLeod, Sargent et al. 2010). A GWAS by Fernandez-Rozadilla et al in 221 CRC patients and a validation set of 791 patients who had been treated with 5-FU with/without oxaliplatin (FOLFOX), showed that 7 SNPs including rs16857540, rs2465403, rs10876844, rs10784749, rs17626122, rs7325568 and rs4243761 associated with adverse drug reactions (ADRs)(Fernandez-Rozadilla, Cazier et al. 2013).

Conclusion

Colorectal cancer remains an important cause of cancer related mortality, despite extensive efforts to treat the disease. In advanced stages, CRC therapy is based on systemic administration of anticancer drugs. But systemic anticancer therapies have limitations including drug resistance and life-threatening side effects. Therefore, researchers are trying to find biomarkers that act as a tool to select the optimal drug type and appropriate dose with the lowest possible toxicity, based on individual's characteristics.

The major obstacle in designing anticancer regimens is genetic variation among individuals and various patterns of gene expression. Although the concept of cancer therapy base on individual's DNA sequences has not yet been accepted as a standard approach clinically, however it is the title of innumerable sciences articles. A large number of publications have shown that polymorphism in the genes responsible for activating, metabolizing, and determining the drug concentration in the cell plays an important role in determining the treatment outcome. It seems that in the future development of molecular pharmacological, biotechnology and genetics revolutionize the principles of anti-cancer therapy based on individual's characteristics.

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Table 1: SNPs and their relationship to CRC anticancer drug treatment outcomes

Gen	Genotype	Variant	Effect	Treatment Regime	Subjects Number	Ref
ABCB1	CT	rs1045642	↑Risk of CRC ↓Time to recurrence	FOLFOX, Xelox, LV5–FU2 and FUP	1028 CRC patients and 1230 controls.	(Wu, Kang et al. 2013)
ABCB1	GT GA	rs2032582	↑Risk of CRC	FOLFOX, Xelox, LV5–FU2 and FUP	1028 CRC patients and 1230 controls.	(Wu, Kang et al. 2013)
ABCB1	T T T	rs1045642 rs1128503 rs2032582 haplotype	↑Risk of CRC	FOLFOX, Xelox, LV5–FU2 and FUP	1028 CRC patients and 1230 controls.	(Wu, Kang et al. 2013)
ABCB1	CT	rs1128503	↑OS	FOLFOX, Xelox, LV5–FU2 and FUP	1028 CRC patients and 1230 controls.	(Wu, Kang et al. 2013)
ABCB1	TT-TT-TT	rs1128503 rs2032582 rs1045642 haplotype	↓ PFS ↑Recurrence-Free Survival	FOLFOX, Xelox, LV5–FU2 and FUP	1028 CRC patients and 1230 controls.	(Wu, Kang et al. 2013)
ABCB1		rs1045642	No Effect	Oxaliplatin and Fluoropyrimidine-Based Adjuvant Chemotherapy	202 (stage II and III) Validation set: independent cohort of 177 patients	(Custodio, Moreno-Rubio et al. 2014)
ABCB1	GT	rs2032582	↑Levels of SN-38	irinotecan with/without cisplatin-	Monotherapy: 55 combination therapy: 62	(Sai, Saito et al. 2010)
ABCB1	G > T/A	rs2032582	↑OS	FOLFIRI	71	(De Mattia, Toffoli et al. 2013)
ABCB1	ABCB1	rs1045642	↑Risk of toxicity	irinotecan and 5-FU	140	(Glimelius, Garmo et al. 2011)
ABCB1	T-T-T	rs1128503 rs2032582 rs1045642 haplotype	↓OS	irinotecan and 5-FU	140	(Glimelius, Garmo et al. 2011)
ABCB1		rs1045642	No Effect	5FU and leucovorin	201	(Huang, Fang et al. 2008)
ABCC2	CC	rs717620	Longer PFS	FOLFIRI	61	(Akiyama, Fujita et al. 2012)
ABCC10	minor alleles	rs2125739	↑Risk of death	oxaliplatin	623 (201 patients received oxaliplatin)	(Kap, Seibold et al. 2016)
ABCG2		rs2231142	No Effect	Oxaliplatin and Fluoropyrimidine-Based Adjuvant Chemotherapy	202 (stage II and III) Validation set: independent cohort of 177 patients	(Custodio, Moreno-Rubio et al. 2014)
ABCG2		rs2728124	No Effect	Oxaliplatin and Fluoropyrimidine-Based Adjuvant Chemotherapy	202 (stage II and III) Validation set: independent cohort of 177 patients	(Custodio, Moreno-Rubio et al. 2014)
ABCG2		rs3114018	No Effect	Oxaliplatin and Fluoropyrimidine-Based Adjuvant Chemotherapy	202 (stage II and III) Validation set: independent cohort	(Custodio, Moreno-Rubio et al. 2014)

					of 177 patients	
ABCG2	C > T	rs7699188	Predictive of the RR	FOLFIRI	71	(De Mattia, Toffoli et al. 2013)
SLCO1B1	GA/AA	rs2306283	Higher rapid response rate ↑PFS	FOLFIRI or mCapeIRI	137	(Huang, Zhang et al. 2013)
SLC19A1	GG	rs1051266	Higher rapid response rate	FOLFIRI or mCapeIRI	137	(Huang, Zhang et al. 2013)
Intergenic	GT	rs6983267	Significant evidence of relative retention		194 paired normal and CRC DNA samples validation set : 296 paired samples	(Gerber, Hampel et al. 2012)
ANXA11	TT	rs1049550	Greater chemosensitive	Bevacizumab+ FOLFIRI	98	(Kim, Kim et al. 2011)
LINS1	G	rs11247226	Greater chemosensitive	Bevacizumab + FOLFOX	98	(Kim, Kim et al. 2011)
DFNB31	GG	rs2274159	Greater chemosensitive	Cetuximab + FOLFIRI	98	(Kim, Kim et al. 2011)
LIFR	GG	rs3729740	Greater chemosensitive	Cetuximab + FOLFIRI	98	(Kim, Kim et al. 2011)
EGFR	GG	rs1050171	↑PFS	Cetuximab and/or Panitumumab	98	(Bonin, Donada et al. 2016)
ERCC1	CC	rs11615	↑PFS	FOLFOX-4	157	(Huang, Huang et al. 2011)
ERCC1	CT & TT	rs11615	↑DFS versus CC	FOLFOX	210	(Zaanan, Dalban et al. 2014)
ERCC2	one variant allele	rs1052559	↓OS	oxaliplatin based chemotherapy	59	(Le Morvan, Smith et al. 2007)
ERCC2	AC	rs13181	↑risk of recurrence	5FU and leucovorin	201	(Huang, Fang et al. 2008)
ERCC2	AA	rs13181	↑PFS	mFOLFOX6	63	(Kumamoto, Ishibashi et al. 2013)
ERCC5	AA	-763AA	↑PFS and OS	oxaliplatin-based chemotherapy	170	(Chen, Luo et al. 2016)
ERCC5	GG	+25GG	↑PFS and OS	oxaliplatin-based chemotherapy	170	(Chen, Luo et al. 2016)
XRCC1	GG	rs25487	↑PFS and OS	FOLFOX-4	157	(Huang, Huang et al. 2011)
XRCC1	AA	rs25487	↑DFS versus GG & GA	FOLFOX	210	(Zaanan, Dalban et al. 2014)
MTHFR	C>T	rs1801133	No effect on prediction ↓Toxicity in 5-FU treatment.	5-FU/leucovorin	331 (stage II–III) 37 stage IV	(Afzal, Jensen et al. 2009)
MTHFR	TT	rs1801133	No effect	oxaliplatin-based	202 (stage II and III) Validation set: 177 (cohort)	(Custodio, Moreno-Rubio et al. 2014)
MTHFR	A>C	rs1801131	Do not predict efficacy of adjuvant 5-FU	5-FU/leucovorin	331 (stage II–III) 37 stage IV	(Afzal, Jensen et al. 2009)
MTHFR	C>T	rs1801133	No effect	5-FU/leucovorin	201	(Huang, Fang et al. 2008)
Selectin E	G>A GG	rs3917412	↑Risk for recurrence	oxaliplatin-based	202 (stage II and III) Validation set: 177 (cohort)	(Custodio, Moreno-Rubio et al. 2014)
topo-1	AA,AC,CC	rs6072249	No effect	FOLFIRI ± bevacizumab	105	(Paolicchi, Vivaldi et al. 2016)
topo-1	AA,AG,GG	rs34282819	No effect	FOLFIRI ± bevacizumab	105	(Paolicchi, Vivaldi et al. 2016)
ATP1A1	minor allele	rs975351	↓Risk of death	oxaliplatin	623 (201 patients received oxaliplatin)	(Kap, Seibold et al. 2016)
ATP8B3	minor allele	rs7249302	↓Risk of death	oxaliplatin	623 (201 patients received oxaliplatin)	(Kap, Seibold et al. 2016)
ATP1B2	minor allele	rs1642763	↓Risk of death	oxaliplatin	623 (201 patients received oxaliplatin)	(Kap, Seibold et al. 2016)
ATP8B3	minor allele	rs8100856	↓Risk of death	oxaliplatin	623 (201 patients received oxaliplatin)	(Kap, Seibold et al. 2016)

GSTP1	AA	rs1695	↓OS in men	oxaliplatin	98	(Sarasqueta, van Lijnschoten et al. 2011)
GSTP1		rs1695	No effect on event-free and OS	oxaliplatin or irrinotecan based chemotherapy	107	(Le Morvan, Smith et al. 2007)
GSTP1		rs1695	No effect on DFS	FOLFOX	210	(Zaanan, Dalban et al. 2014)
GSTP1	AA	rs1695	poor responses	mFOLFOX6	63	(Kumamoto, Ishibashi et al. 2013)
GSTM1 Deletion	One copy		↑OS	Chemotherapy for 36.4 months. 65 patients received oxaliplatin	338	(Funke, Timofeeva et al. 2010)
GSTM5	minor alleles	rs11807	↑risk of death	oxaliplatin	623 (201 patients received oxaliplatin)	(Kap, Seibold et al. 2016)
UGT1A1	28 allele	rs8175347	↓RR	irrinotecan	94	(Marcuello, Paez et al. 2011)
UGT1A1	28 allele	rs8175347	No association with RR	irrinotecan	1898	(Dias, McKinnon et al. 2012)
TYMS		rs45445694	protein expression, clinical benefit, adverse effects		2402	(Jennings, Kwok et al. 2012)
TYMS		double or triple tandem repeats	No effect	5-FU and leucovorin	201	(Huang, Fang et al. 2008)

Table 2 :SNPs and their relationship to toxicity following CRC anticancer drugs						
Gen	**genotype**	**Variant**	**Effect**	**Treatment Regime**	**Number of Subjects**	**Ref**
ABCC5	CC	rs562	GI Toxicity	Irinotecan	26	(Di Martino, Arbitrio et al. 2011)
ABCG1	GG	rs425215	GI Toxicity	Irinotecan	26	(Di Martino, Arbitrio et al. 2011)
ABCG2		rs7699788	Nonhematological	FOLFIRI	71	(De Mattia, Toffoli et al. 2013)
OaTP1B1/ SLCO1B1	GA	rs2306283	GI Toxicity	Irinotecan	26	(Di Martino, Arbitrio et al. 2011)
UGT1A1	C>T	homozygous 3156	Neutropenia	IROX	520	(McLeod, Sargent et al. 2010)
UGT1A1	28 allele	rs8175347	Neutropenia	IROX	520	(McLeod, Sargent et al. 2010)
UGT1A	28 allele	rs8175347	Hematologic Toxicity Febrile Neutropenia		167	(Lévesque, Bélanger et al. 2013)
UGT1A	1A9/1A7/ 1A1 haplotype HII	UGT1A1*28	Neutropenia	5-U/Irinotecan-Based regimen	167	(Lévesque, Bélanger et al. 2013)
UGT1A		rs2070959	Neutropenia	5-U/Irinotecan-Based regimen	167	(Lévesque, Bélanger et al. 2013)
UGT1A		rs11692021	Neutropenia	5-U/Irinotecan-Based regimen	167	(Lévesque, Bélanger et al. 2013)
UGT1A		UGT1A9 c.-688	Neutropenia	5-U/Irinotecan-Based regimen	167	(Lévesque, Bélanger et al. 2013)
GSTM1		Deletion	Neutropenia	FOLFOX	520	(McLeod, Sargent et al. 2010)
GSTP1		Homozygous Variant Genotype	Neurotoxicity	FOLFOX	520	(McLeod, Sargent et al. 2010)
GSTP1	AA	rs1695	Neurotoxicity	FOLFOX	520	(McLeod, Sargent et al. 2010)
DPYD	G/A	rs1801160	Neutropenia	FOLFOX-4 / XELOX	195	(Graziano, Ruzzo et al. 2016)
DPYD	G/A	rs3918290	Neutropenia	FOLFOX-4 / XELOX	195	(Graziano, Ruzzo et al. 2016)
DPYD	C/T	rs1801265	Diarrhoea	FOLFOX-4 / XELOX	195	(Graziano, Ruzzo et al. 2016)
DPYD	T>A	464	Diarrhoea, Mucositis Leucopoenia Thrombocytopaenia, Dehydration	5-FU / Leucovorin	a 73-year-old woman	(Morel, Boisdron-Celle et al. 2007)
DPYD	A/A A/G	rs3918290	Nausea/Vomiting Neutropenia	FOLFOX or FOLFIRI ±cetuximab	2886 (stage III)	(Lee, Shi et al. 2014)
DPYD	A>T	rs67376798	Dehydration Diarrhea Leukopenia Neutropenia Thrombocytopenia	FOLFOX or FOLFIRI ±cetuximab	2886 (stage III)	(Lee, Shi et al. 2014)

NLGN1		rs16857540	Mucositis	5-FU	221 validation set: 791	(Fernandez-Rozadilla, Cazier et al. 2013)
COLEC10		rs2465403	Mucositis	5-FU	221 validation set: 791	(Fernandez-Rozadilla, Cazier et al. 2013)
PARD3B		rs17626122	Haematologic	FOLFOX	221 validation set: 791	(Fernandez-Rozadilla, Cazier et al. 2013)
Intergenic Locations		rs10876844	Diarrhoea	5-FU	221 validation set: 791	(Fernandez-Rozadilla, Cazier et al. 2013)
Intergenic Locations		rs10784749	Diarrhoea	5-FU	221 validation set: 791	(Fernandez-Rozadilla, Cazier et al. 2013)
Intergenic Locations		rs7325568	Haematologic	FOLFOX	221 validation set: 791	(Fernandez-Rozadilla, Cazier et al. 2013)
Intergenic Locations		rs4243761	Haematologic	FOLFOX	221 validation set: 791	(Fernandez-Rozadilla, Cazier et al. 2013)